Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/830,190	ANNAPRAGADA ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

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10/830,190	04/21/2004	Ananth Annapragada	27428-4	7714

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	**PAPER NUMBER**
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08/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/830,190	ANNAPRAGADA ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-11 and 25-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-11 and 25-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-4,6-11 and 25-33 are pending in the application. Any objections and/or rejections from previous office actions that have not been reiterated in this office action are obviated.

1. The declarations under 37 CFR 1.132 filed 8/9/07 are sufficient to overcome the rejection of claims 1-4,6-10 and 25-32 under 35 U.S.C. 102(a) as being anticipated by Kao et al. *(Acad. Radiol.* **2003**, *10*, 475-483) based upon the co-ownership of the subject matter of the published article and the invention and also that the author Kenneth C. Beck is not an inventor of the invention of the current application.

Response to Arguments

1. Applicant's arguments filed 8/9/07 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 33 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as stated in the office action mailed 5/9/07.

4. Applicant asserts that broad ranges disclosed in the specification adequately provide support for the narrow ranges of the instant claim. For example, applicant

asserts that the range of 60-70% disclosed for the one first lipid or phospholipids HSPC adequately provides support for the narrow range of about 58 to about 59% recited in the instant claim, etc..

5. The broad ranges described in the specification do not exactly provide the narrow ranges recited in the claims.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as stated in the office action mailed 5/9/07.

8. Applicant asserts that amendment to the instant claim distinctly claims the subject matter which applicants regard as their invention.

9. The recitation of "essentially free" is unclear and confusing as there is no definition of what constitutes "essentially free" in the specification.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-4,7-14,25,27-29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leike et al. (*Invest. Radiol.* **2001**, *36*, 303-308) in view of Torchilin et al. (*Biochim. Biophys. Acta* **1996**, *1279,* 75-83) or Sachse et al. (*Invest. Radiol.***1997**, *32*, 44-50) as stated in the office action mailed 5/9/07. The modified rejection was necessitated by the amendment.

12. Applicant asserts that Leike et al. teaches unmodified (conventional) iopromide-carrying blood-pool liposomes which do not have a diameter of less than about 150 nm.

13. The reference of Leike et al. was not used to teach of the modified iopromide-carrying blood-pool liposomes but to teach that iopromide-carrying blood-pool liposomes have been used for computed tomography blood-pool imaging. The liposomes of Leike et al. were of the size 201 nm.

14. Applicant asserts that Leike et al. does not teach the removal of unencapsulated contrast agent.

15. The examiner concedes that Leike et al. does not teach the removal of unencapsulated contrast agent.

16. Applicant asserts that Torchilin et al. teaches radioactively labeled liposomes and does not teach the use of non-radioactive contrast enhancing agents.

17. The reference of Torchilin et al. was not used to teach the use of non-radioactive contrast enhancing agents but to teach of the preparation of liposomes from a mixture of PC, cholesterol and PEG-PE. The resulting small liposomes are of the size 120-150 nm (p77, preparation of liposomes). In the case of small liposomes, the grafting of PEG to the liposome surface sharply increases the liposomal circulation time due to the

interaction of the PEG with plasma proteins (p80, small liposomes). In fact, Torchilin et al. teaches that the blood circulation time for PEG-LL (large liposomes) is less than that for PEG-SL (small liposomes) (p81, paragraph 1).

18. In view of the combined references of Leike et al. and Torchilin et al. it would have been obvious to one ordinarily skilled in the art to PEGylate the liposomes for CT imaging of the vasculature Leike et al. as the blood circulation time of the liposomes are improved by coating the surface with PEG by decreasing their opsonization and recognition by the liver Torchilin et al. The small sizes of sterically stabilized liposomes are advantageous as they have longer blood circulation times. Therefore it would be obvious to try to PEGylate the liposomes of Leike et al. with sizes of 120-150 nm.

19. Applicant asserts that Sachse et al. does not teach the removal of the unencapsulated contrast agent.

20. The examiner concedes that Sachse et al. does not teach the removal of unencapsulated contrast agent.

21. Claims 1-4,6-11 and 25-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness et al. (US 5,676,928) or Tournier et al. (US 6,217,849B1) in view of Torchilin et al. (*Biochim. Biophys. Acta* **1996**, *1279,* 75-83) as stated in the office action mailed 5/9/07. The modified rejection was necessitated by the amendment.

22. Applicant asserts that Klaveness et al. does not disclose a pharmaceutically acceptable excipient or sterically bulky excipient capable of stabilizing sterically stabilized liposomes in blood.

23. The reference of Klaveness et al. does teach of pharmaceutically acceptable excipients and the resulting liposome suspensions are stable in the blood and on storage (column 4, lines 41-42). Therefore any excipients added to the suspensions must be capable of stabilizing the suspensions in the blood as well as for storage. The average particles size of the liposomes is 50-3000 nm, preferably 150 nm.

24. Applicant asserts that Klaveness et al. is undeniably based on an autoclaving step.

25. The examiner concedes that the liposome suspension of Klaveness et al. include an autoclaving step.

26. Applicant asserts that Klaveness et al. does not provide a single instance of the use of the polymer-derivatized lipid or phospholipids but states that the composition of the invention, for use in any type of imaging, may if desired be modified with materials such as PEG to increase the circulation half-life of the liposomes.

27. The instant claims are not drawn to the method of use of the liposomes and the sterically stabilized liposomes of Klaveness et al. in combination with the reference of Torchilin et al. encompass the liposomes of the instant claims where the size is less than about 150 or 120 nm.

28. Applicant asserts that Tournier et al. teaches vesicles of 200 nm to 1 μm and that Tournier et al. does not make, use or even desire to make or use vesicles having a diameter of less than about 150 nm.

29. Tournier et al. discloses that liposome suspensions in the field of imaging are known to be about 100 nm in size. Torchilin et al. teaches of the preparation of liposomes from a mixture of PC, cholesterol and PEG-PE. The resulting small liposomes are of the size 120-150 nm (p77, preparation of liposomes). In the case of small liposomes, the grafting of PEG to the liposome surface sharply increases the liposomal circulation time due to the interaction of the PEG with plasma proteins (p80, small liposomes). In fact, Torchilin et al. teaches that the blood circulation time for PEG-LL (large liposomes) is less than that for PEG-SL (small liposomes) (p81, paragraph 1). In combination with the reference of Tournier et al. it would be obvious to make sterically stabilized liposomes of the size 100-150 nm. Also the reference of Tournier et al. was utilized to teach of the liposomes suspensions which may be prepared without the contrast agent in the suspension media.

30. Applicant asserts that Torchilin et al. is irrelevant since it teaches radioactively labeled liposomes.

31. The reference of Torchilin et al. was not used to teach the use of non-radioactive contrast enhancing agents but to teach of the preparation of liposomes from a mixture of PC, cholesterol and PEG-PE. The resulting small liposomes are of the size 120-150 nm (p77, preparation of liposomes). In the case of small liposomes, the grafting of PEG to the liposome surface sharply increases the liposomal circulation time due to the

interaction of the PEG with plasma proteins (p80, small liposomes). In fact, Torchilin et al. teaches that the blood circulation time for PEG-LL (large liposomes) is less than that for PEG-SL (small liposomes) (p81, paragraph 1).

Conclusion

No claims are allowed at this time.

32. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MP
August 15, 2007

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER